

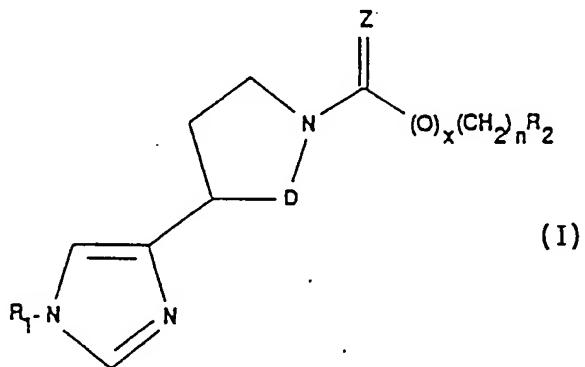
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(54) Title: 4-[4'-PIPERIDINYLPYRROLIDINYL] SUBSTITUTED IMIDAZOLES AS H3-RECEPTOR ANTAGONISTS AND THERAPEUTIC USES THEREOF



(57) Abstract

The present invention provides novel compounds having activity as histamine H₃-receptor antagonists. In a preferred aspect, the compounds of the invention exhibit ready penetration of the blood-brain-barrier and reduced toxicity. The novel compounds of the invention include compounds of the formula (I) wherein D is CH₂ or CH₂-CH₂, Z represents S or O, preferably O, x is 0 or 1, n is an integer from 0 to 6, R₁ represents preferably hydrogen, or a hydrolysable group, but can be a lower alkyl or aryl group, and R₂ represents a linear chain, branched chain or carbocyclic group or aryl group of up to about 20 carbon atoms, and salts thereof. If R₂ is tert-butyl, cyclohexyl, or dicyclohexylmethyl, x or n must not be 0. If R₂ is adamantane, the sum of x and n must be greater than 1. The various alkyl or aryl groups can have functional group substituents. Illustrative of the compounds of the invention is the molecule 4-(1-cyclohexylvaleryl)-1H-imidazole.

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4-[4'-PIPERIDINYL OR 3'-PIRROLIDINYL] SUBSTITUTED IMIDAZOLES AS H3-RECEPTOR ANTAGONISTS AND THERAPEUTIC USES THEREOF

5 The present application is a continuation-in-part of application Serial No. 07/862,657, filed April 1, 1992, which is incorporated herein by reference in its entirety.

1. FIELD OF THE INVENTION

10 The present invention relates to novel compounds having potent activity as histamine H₃-receptor ("H₃") antagonists, and methods of using such compounds.

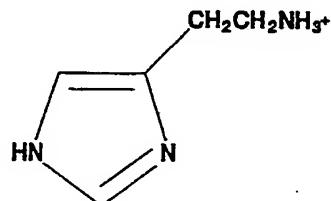
2. BACKGROUND OF THE INVENTION

15 Dementias tend to be characterized by cognitive disorders and often by depression. A particularly devastating dementia is Alzheimer's disease (AD). AD affects more than 30% of humans over 80 years of age, and as such, represents one of the most important health problems in developed countries (Evans et al., J.A.M.A. 262: 2551-2556 (1989); Katzman and Saitoh, FASEB J. 280: 278-286 (1991)). This neurodegenerative disorder of unknown etiology is clinically characterized by gradual impairment of cognitive function. The large buildup of intracytoplasmic neurofibrillary tangles and neurite plaques observed 20 histopathologically in AD plausibly leads to degeneration of affected nerve cells. At least one study showed decreases in histamine and histidine levels in frontal, temporal and occipital cortices and 25 in the caudate nucleus of brains from AD patients examined post mortem (Mazurkiewics and Wsonwah, Can. J. Physiol. Pharmacol., 67:75-78 (1989)).

30 Histamine is a chemical messenger involved in various complex biological actions. It is widely distributed in the plant and animal kingdoms. In 35 mammals, including man, it occurs mainly in an inactive bound form in most body tissues. When

released, histamine interacts with specific macromolecular receptors on the cell surface or within a target cell to elicit changes in many different 5 bodily functions. Histamine (4(2-aminoethyl) imidazole) is a base. Its chemical structure is:

10



Histamine receptor pharmacology has revealed three 15 subtypes of receptors which mediate (or are associated with) the activity of histamine. These receptors are most commonly referred to as H_1 , H_2 , and H_3 . The most recently discovered of these receptors is the H_3 , histamine receptor. Early studies suggested the presence of another histamine receptor when it was 20 demonstrated that histamine inhibits its own synthesis and release in brain slices by a negative feedback process operating at the level of histaminergic nerve-endings (see, for example, Arrang, J.M. *et al.* *Nature* 302:832-837 (1983)). More recently, the H_3 receptor 25 has been shown to function as a pre-synaptic autoreceptor inhibiting histamine synthesis and histamine release from neurons, especially in the control nervous system (Arrang, *et al.* *Nature* 327:117-123 (1987)). The presence of H_3 receptors in 30 peripheral tissues has also been reported and here too they appear to be involved with the nervous system. Thus, histamine depresses sympathetic neurotransmission in the guinea pig mesenteric artery by interacting with H_3 receptors on the perivascular nerve 35 terminals (Ishikawa and Sperelakis, *Nature* 327:158 (1987)). This important observation suggests that

histamine may control the release of other neurotransmitters (Tamura et al., *Neuroscience* 25:171 (1988)). Inhibitory histamine H₃ receptors also exist
5 in the guinea pig ileum where their role appears to be to modify the magnitude of histamine contraction, rather than affecting histamine release (Trzeciakowski, *J. Pharmacol. Exp. Therapy* 243:847 (1987)). Particularly intriguing is the discovery of
10 H₃ receptors in the lung (Arrang et al. supra (1987)). The presence of histamine H₃ receptors in the lung raises the question of whether they control histamine release in anaphylaxis and whether they may be manipulated to provide therapy in asthma. Indeed it
15 has been suggested that H₃ receptors may have a modulating role on excitatory neurotransmission in airways. Generally, however, H₃ receptor inhibition tends to increase histamine activity, with potentially detrimental effects. Thus, it is desirable to avoid
20 introducing H₃ receptor antagonists that act on peripheral tissues.

Histamine H₃ receptor activation was found to inhibit acetylcholine release in a guinea pig ileum model (Poli et al., *Agents and Actions* 33: 167-169).
25 Selective H₃-receptor blockers reversed the histamine-induced inhibitory effect. Histamine also decreased serotonin release; this effect was reversed with an H₃-antagonist, and was suggested to operate via the histamine H₃-receptors (Schlicker et al., *Naunyn-Schmiedaberg's Arch. Pharmacal.* 337: 588-590 (1988)). Activation of H₃-receptors was found to inhibit excitatory presynaptic potentials (Arrang et al., *J. Neurochem.* 51:105 (1988)).

One reported highly specific competitive
35 antagonist of histamine H₃ receptors is thioperamide (Arrang et al., supra (1987)). Although thioperamide

is a very potent antagonist *in vitro* ($K_i = 4.3 \text{ nmol/L}$), relatively high doses are required *in vivo* to inhibit histamine release from the brain in rats (Ganellin *et al.*, *Collect. Czech. Chem. Commun.* **56**:2448-2455 (1991)). Ganellin *et al.* suggests that this most probably results from poor penetration through the blood-brain-barrier by this peramide, although the pharmacokinetic properties of thioperamide may also play a role. Moreover, the thiourea functionality found in thioperamide may result in higher intrinsic toxicity of thioperamide.

Thiourea-containing drugs are known to be associated with undesirable side effects in clinical use. For example, with thiourea-containing drug molecules that are used to treat hyperthyroidism, agranulocytosis is known to be a serious, and occasionally fatal, toxic effect in clinical use (see, e.g., Brimblecombe *et al.* *Gastroenterology* **74**:339-346 (1978)). The thiourea-containing histamine H₂-receptor antagonist metiamide caused a low incidence of granulocytopenia in peptic ulcer patients and was withdrawn from clinical use (Forrest *et al.*, *Lancet* **1**: 392-393 (1975)). In high dose, repeated dose toxicological studies in dogs, incidences of agranulocytosis were seen at 162 mg/kg/day (Brimblecombe *et al.*, "Toxicology of Metiamide," *International Symposium on Histamine H₂ - Receptor Antagonists*, Wood and Simpkins, Smith Kline & French, pp. 53-72 (1973)). A proportion of dogs (<10%) died acutely with pulmonary edema and pleural effusion. The metiamide isostere cimetidine, in which the thiourea group was replaced by an alternative group (cyanoguanidine), did not cause granulocytopenia, or any other side effects in animal toxicity studies or in clinical usage by multimillions of patients,

indicating that the toxicological problems with metiamide could be attributed to the presence of the thiourea group (Brimblecomb *et al.*, *supra*). It is 5 likely that the thiourea functionality, with its association with toxicological phenomena and its likelihood of inducing undesirable side effects, could limit the clinical development of thioperamide.

Although some predictions have been made 10 concerning the ability of molecules to pass through the blood brain barrier, these predictions are at best speculative. The rate and extent of entry of a compound into the brain are generally considered to be determined primarily by partition coefficient, 15 ionization constant(s) and molecular size. No single partition solvent system has emerged as a universally applicable model for brain penetration, although the octanol water system has received particular attention, and Hansch and coworkers have suggested 20 that a partition coefficient in this system of about 100 is optimal for entry into the central nervous system (CNS) (Glave and Hansch, *J. Pharm. Sci.*, 61:589 (1972); Hansch *et al.*, *J. Pharm. Sci.*, 76:663 (1987)). Comparisons between known H₂ antagonists, however, 25 suggest that there is no such simple relationship between their brain penetration and octanol water partition coefficients (Young *et al.*, *J. Med. Chem.* 31:656 (1988)). The comparison of the ability of histamine H₂ receptor antagonists to cross the blood 30 brain barrier suggests that brain penetration may increase with decreasing over-all hydrogen binding ability of a compound (Young *et al.*, *supra*). However, optimizing H₂ receptor antagonists to improve brain penetration reduced antagonist potency (Young *et al.*, 35 *supra*). Thus it is fundamentally difficult to

optimize both blood brain barrier permeability and function of a compound.

It is therefore an object of the present invention to provide novel potent histamine H₃-receptor antagonists that are better able to penetrate the blood-brain-barrier than previously reported compounds.

Further it is an object of the present invention to provide novel potent histamine H₃-receptor antagonists that have reduced toxicity compared to other known H₃ antagonists.

Another object of the present invention is to provide histamine H₃-receptor antagonists that will act selectively on the brain and have limited activity on H₃ receptors in peripheral tissues.

It is yet another object of the present invention to provide a novel class of histamine H₃-receptor antagonists.

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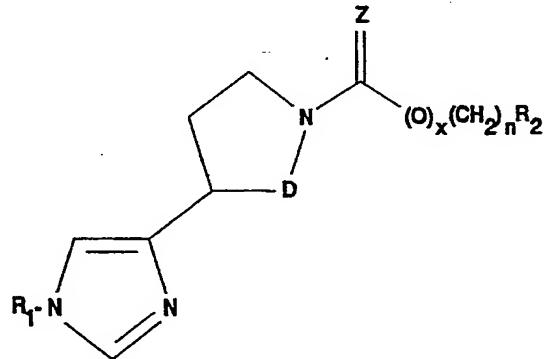
3. SUMMARY OF THE INVENTION

The present invention provides novel compounds having activity as histamine H₃-receptor antagonists.

In a preferred aspect, the compounds of the invention exhibit ready penetration of the blood-brain-barrier and reduced toxicity. The novel compounds of this invention include compounds of the formula:

30

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wherein D is CH₂ or CH₂-CH₂, Z represents S or O, preferably O, x is 0 or 1, n is an integer from 0 to 6, R₁ represents preferably hydrogen, or a hydrolyzable group, but can be a lower alkyl or aryl group, and R₂ represents a linear chain, branched chain or carbocyclic group or aryl group of up to about 20 carbon atoms, and salts thereof. If R₂ is tert-butyl, cyclohexyl, or dicyclohexylmethyl, x or n must not be 10 0. If R₂ is adamantane, the sum of x and n must be greater than 1. The various alkyl or aryl groups can have functional group substituents.

It has been discovered that amide or carbamate functional groups can be used to join alkyl or aryl 15 substituents to the piperidyl nitrogen of 4(4-piperidyl)-1H-imidazole groups. Other cyclic imides, particularly pyrrolidyl or cycloheptamidyl (C₆H₁₁N) can be substituted for piperidine. In a preferred aspect, the compounds of the invention are surprisingly 20 effective at transport across the blood brain barrier, thus limiting their effects primarily to cerebral histamine H₃-receptors, and are also less toxic than histamine H₃-receptor antagonists based on a thiourea functional group.

In addition, the present invention encompasses a pharmaceutical composition comprising a compound of the invention, and a method of using a compound or pharmaceutical composition of the invention in an animal, particularly in a human, to treat Alzheimer's 25 disease and other dementias by ameliorating the cognitive defects and neurodegenerative effects associated therewith. The histamine H₃-receptor antagonists of the invention have additional therapeutic uses where increased arousal and attention 30 is desired.

4. BRIEF DESCRIPTION OF THE FIGURES

FIG. 1. Binding of N ^{α} -methylhistamine to rat cortical homogenate. Open box: total bound; x'ed box: specific binding; closed box: non-specific binding.

FIG. 2. Binding of ³H-labeled N ^{α} -methylhistamine to the cortical homogenate of thioperamide injected rats.

10 FIG. 3. Binding of ³H-labeled N ^{α} -methylhistamine to the cortical homogenate of compound 1 injected rats.

FIG. 4. The effect of α -methylhistamine on sleeping one hour after injection.

15 FIG. 5. The effect (dose-response) of thioperamide on sleep induced by R(-)- α -methylhistamine (30 mg/kg).

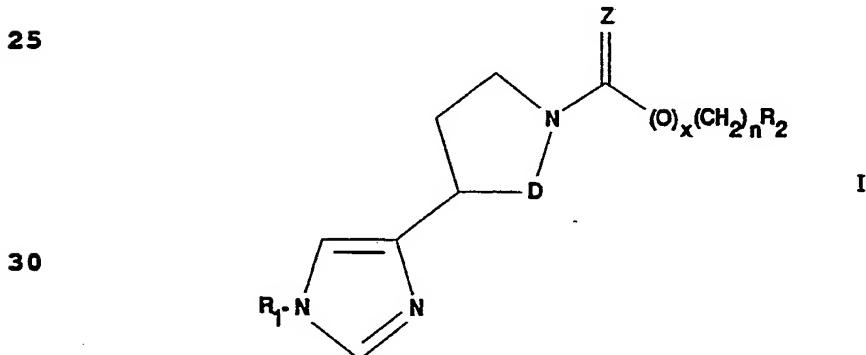
FIG. 6. The effect (dose-response) of compound 1 on sleep induced by R(-)- α -methylhistamine (25 mg/kg).

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5. DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are compounds of the general formula.

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wherein D is CH₂ or CH₂-CH₂, Z represents sulfur (S) or 35 oxygen (O), preferably O, x is 0 or 1, n is an integer from 0 to 6, R₁ represents hydrogen, an in vivo

hydrolizable group, a lower alkyl group, a lower cyclic alkyl group, or a lower aryl group, and R₂ represents a substituted or unsubstituted linear chain or branched chain alkyl group of up to about 20 carbon atoms, a substituted or unsubstituted carbocyclic group of up to about 20 carbon atoms including mono and bicyclic moieties, and a substituted or an unsubstituted aryl group of up to about 20 carbon atoms, or any combination of above-mentioned groups, or salts thereof. In a specific embodiment, R₂ can represent a disubstituted methyl, such as but not limited to dicyclohexyl methyl (-CH(C₆H₁₁)₂), diphenyl methyl (-CH(C₆H₅)₂), and the like. If R₂ is tert-butyl, cyclohexyl, or dicyclohexylmethyl, x or n must not be 0. If R₂ is adamantane, the sum of x and n must be greater than 1.

In a preferred embodiment, R₁ is hydrogen. It is also contemplated that R₁ can be a hydrolyzable leaving group, such as an acyl or carbamyl, including where R₁=-CZ(O)_x(CH₂)_nR₂, as in I above. It is well known that N-acylimidazoles are hydrolytically labile, and R₁ may be selected such that it yields the parent imidazole compound *in vivo* at an optimal rate. Such hydrolysis will yield the compound with hydrogen as R₁. Thus, the contemplated compounds of the invention with a hydrolyzable substituent at R₁ are functionally equivalent to the preferred embodiment, i.e., where R₁ is hydrogen. R₁ can also be a lower linear chain, branched chain, or cyclic alkyl, or a lower aryl. The term "lower" as applied to the alkyl or aryl substituents at R₁ indicates the presence of up to seven carbon atoms. In specific embodiments infra, R₁ is methyl, benzyl, methylcyclohexane, N-cyclohexylformamide, benzaldehyde, and t-butylaldehyde.

In yet a further embodiment, the nitrogen atom at position 3 of the imidazole ring can be substituted with a lower alkyl or aryl group, or with a 5 hydrolyzable leaving group.

In a preferred embodiment, D is $\text{CH}_2\text{-CH}_2$, resulting in a piperidine ring structure. However, it is contemplated that D can be CH_2 , yielding a pyrrolidine ring structure. In yet another embodiment, D can be 10 $(\text{CH}_2)_3$, yielding a cycloheptimide (seven membered heterocycle with one nitrogen). While orientation of the imidazole group distal to the N of the piperidine is preferred, the invention contemplates the imidazole at the 2 or 3 position on the piperidine (or the 2 15 position of pyrrolidine, or the 2 and 3 position of the cycloheptimide ring). These alternate embodiments can be used instead of the piperidyl embodiment with the imidazole group located at the 4 position, although the piperidyl embodiment is preferred.

20 Although the present invention is not limited to any mechanistic theory, it is believed that the blood brain barrier is permeable to the compounds of the present invention in part because of the subtle decrease in polarity afforded by an amide or carbamate bond linking the $(-(0),_x(\text{CH}_2)_n\text{R})$ moiety (e.g., a 25 hydrophobic tail) to the 4(4-piperidyl)-1H-imidazole (or 4(3-pyrrolidyl)-1H-imidazole) structure. With slightly less polarity and hydrogen-bonding capability than urea or thiourea, the amide or carbamate 30 functionality can more efficiently traverse the blood brain barrier. Moreover, the dipole of the amide or carbamate is distal to the hydrophobic tail, more proximal to the imidazole (which is a fairly polar group), and thus tends to effect greater amphiphilicity 35 in the molecule. That the compounds of the invention retain amphiphilic character is important for

solubility in aqueous solution. Solubility in aqueous solution is desirable for a compound to be used therapeutically in an animal particularly in a human.

- 5 That such a subtle difference, use of an amide or carbamate functionality, should perceptably alter blood brain barrier permeability may be considered to be surprising since it is not generally appreciated.

In preferred embodiments, a bulky hydrocarbon R₂ group is chosen so that the net hydrophilicity of the H₁-receptor antagonist is increased, and the steric effects of a bulky substituent at R₂ are decreased, by increasing the number of methylenes in a straight chain alkyl group (i.e., in Formula I, n > 1). In a specific embodiment, a tetramethylene bound to the amide or carbamate group is used. Preferably a cyclic alkyl or aryl group is linked to the amide or carbamate via the straight chain alkyl group. In a specific embodiment, tetramethylene cyclohexane (cyclohexylbutyl) is bound to an amide. Although specific hydrophobic alkyl and aryl groups have been mentioned, one of ordinary skill in the art will recognize that there are many possible hydrophobic groups for use in the compounds of the invention.

25 These fall within the scope of the instant invention.

Thus, R₂ can be one or more bulky substituent groups. As stated above, in a preferred aspect of the invention, the bulky substituents are removed from the amide or carbanate group on the piperidyl-imidazole by increasing n. In one embodiment, R₂ is CHR₃R₄, in which n is 3 or 4 and R₃ and R₄ are cyclohexyl, phenyl, or the like. R₃ and R₄ can be the same group or different groups. In another embodiment, R₂ is decalin or adamantane or the like. If R₂ is adamantane, 35 preferably n is greater than 1, but the sum of x and n must be greater than 1.

As used herein, the phrase linear chain or branched chained alkyl groups of up to about 20 carbon atoms means any substituted or unsubstituted acyclic 5 carbon-containing compounds, including alkanes, alkenes and alkynes. Examples of alkyl groups include lower alkyl, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl or tert-butyl; upper alkyl, for example, octyl, nonyl, decyl, and the like; 10 and lower alkylene, for example, ethylene, propylene, propyldiene, butylene, butyldiene, and the like. The ordinary skilled artisan is familiar with numerous linear and branched alkyl groups, which are within the scope of the present invention.

15 In addition, such alkyl group may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Functional groups include but are not limited to hydroxyl, amino, carboxyl, amide, ester, ether, and 20 halogen (fluorine, chlorine, bromine and iodine), to mention but a few.

As used herein, substituted and unsubstituted carbocyclic groups of up to about 20 carbon atoms means cyclic carbon-containing compounds, including 25 but not limited to cyclopentyl, cyclohexyl, cycloheptyl, admantyl, and the like. Such cyclic groups may also contain various substituents in which one or more hydrogen atoms has been replaced by a functional group. Such functional groups include 30 those described above, and lower alkyl groups as described above. The cyclic groups of the invention may further comprise a heteroatom. For example, in a specific embodiment, R₂ is cyclohexanol.

As used herein, substituted and unsubstituted 35 aryl groups means a hydrocarbon ring bearing a system of conjugated double bonds, usually comprising six or

more even number of π (pi) electrons. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, anisyl, toluyl, xylenyl and the like.

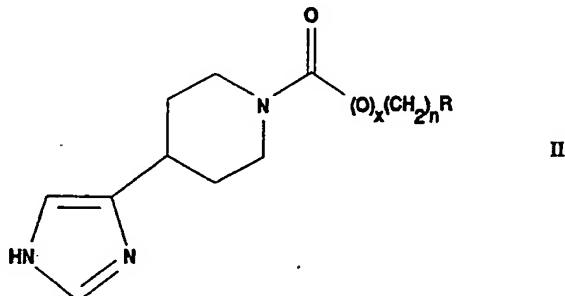
5 According to the present invention, aryl also includes heteroaryl groups, e.g., pyrimidine or thiophene. These aryl groups may also be substituted with any number of a variety of functional groups. In addition to the functional groups described above in connection
 10 with substituted alkyl groups and carbocyclic groups, functional groups on the aryl groups can be nitro groups.

As mentioned above, R_2 can also represent any combination of alkyl, carbocyclic or aryl groups, for
 15 example, 1-cyclohexylpropyl, benzyl cyclohexylmethyl, 2-cyclohexylpropyl, 2,2-methylcyclohexylpropyl, 2,2-methylphenylpropyl, 2,2-methylphenylbutyl.

In a specific embodiment, R_2 represents cyclohexane, and $n=4$ (cyclohexylvaleroyl). In another
 20 specific embodiment, R_2 represents cinnamoyl.

Particularly preferred are compounds of the formula:

25



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wherein x is 0 or 1, n is an integer from 0 to 6, more preferably $n = 3-6$, and most preferably $n=4$, and R is as defined for R_2 above. Examples of preferred alkyl
 35 groups for R include but are not limited to cyclopentyl, cyclohexyl, adamantane methylene,

dicyclohexyl methyl, decanyl and t-butyryl and the like. Examples of preferred aryl and substituted aryl groups include but are not limited to phenyl, aryl 5 cyclohexyl methyl and the like.

5.1. SYNTHESIS OF THE COMPOUNDS

The compounds of the present invention can be synthesized by many routes. It is well known in the art of organic synthesis that many different synthetic protocols can be used to prepare a given compound. Different routes can involve more or less expensive reagents, easier or more difficult separation or purification procedures, straightforward or cumbersome scale-up, and higher or lower yield. The skilled synthetic organic chemist knows well how to balance the competing characteristics of synthetic strategies. Thus the compounds of the present invention are not limited by the choice of synthetic strategy, and any synthetic strategy that yields the compounds described above can be used.

As shown in the Examples, *infra*, two general procedures can be used to prepare the instant compounds. Both involve condensation of an activated (electrophilic) carbonyl with the nucleophilic piperidyl nitrogen of 4-(4-piperidyl)-1H-imidazole.

The first procedure involves preparing the acid chloride derivative or acid anhydride of a carbonyl, i.e., activating the carbonyl. This activated carbonyl is added in molar excess to the piperidyl-imidazole in the presence of a molar excess of an unreactive base, for example, but not limited to, dicyclohexyl amine.

The second procedure is to condense the piperidyl-imidazole with a slight molar excess of a dicarbonate, again in the presence of an unreactive

base, for example and not by way of limitation, triethylamine. This method can be used especially in the preparation of carbamate compounds.

5 A preferred synthesis of the 4-(4-piperidyl)-1H-imidazole is also provided. Commercially available 4-acetyl pyridine (Aldrich Chemical Co.) is converted into the key intermediate 4-(4-pyridyl)-1H-imidazole by bromination with hydrogen bromide in acetic acid
10 (Barlin, et al., *Aust. J. Chem.* **42**:735 (1989)) to yield the bromoacetyl pyridine in high yield. Reaction of bromoacetyl pyridine with formamide at 110°C affords the substituted imidazole in high yield. The reaction is usually performed without the addition of
15 any solvent. The pyridyl moiety is reduced by catalytic hydrogenation using 5-10% Rhodium on carbon in acidified water at a pressure of 20-55 atmospheres to yield 4-(4-piperidyl)-1H-imidazole. This synthesis is disclosed more fully in copending United States
20 patent application Serial No. 07/862,658, filed by the instant inventors on April 1, 1992, entitled "PROCESS FOR THE PREPARATION OF INTERMEDIATES USEFUL FOR THE SYNTHESIS OF HISTAMINE RECEPTOR ANTAGONISTS," which is specifically incorporated herein by reference in its
25 entirety.

Solvents for use in the synthesis of the compounds of the invention are well known in the art. The solvent must be non-reactive, and the starting materials and base must be soluble in the solvent.
30 Preferably, an aprotic organic solvent of medium to high polarity is used. For example, acetonitrile, can be used. Under appropriate conditions, in the synthesis of carbamates of the invention, an alcohol, e.g., methanol, can be used.

35 The electrophilic carbonyl group, which contains the R₂ moiety, can be obtained from commercial sources,

or it may be prepared synthetically. In specific examples, *infra*, the carbonyl is obtained commercially. Activation of carbonyls is well known.

5 The acid chloride can be prepared by reacting the carboxylic acid with sulfonyl chloride. Alternatively, the acid chloride may be available commercially. In specific embodiments, *infra*, acid chlorides were obtained from commercial sources

10 (Aldrich Chemical). Similarly, the acid anhydride can be prepared conveniently by reaction of a salt of the carboxylic acid with the acid chloride. In a specific embodiment, the carboxylic acid is reacted with a carbonate acid chloride to form an asymmetric acid

15 anhydride. In another embodiment, the acid anhydride can be obtained commercially. In a specific embodiment, *infra*, the acid anhydride was obtained from Aldrich Chemical. Dicarbonates for use in the invention are available commercially, e.g., from

20 Aldrich Chemical.

5.2. BIOLOGICAL ACTIVITY

The compounds of the present invention are biologically active in assays for histamine H₃-receptor antagonist activity, as well as in a radioligand binding assay in rat brain membranes (e.g., Table I, *infra*). The binding assay procedure used and its standardization with known H₃-receptor antagonists is shown in the examples *infra*.

30 Further biological studies can demonstrate that the histamine H₃-receptor antagonists of this invention reverse the soporific effects of the histamine H₃-receptor agonist, R(-)-alphamethylhistamine in mice when both drugs are administered peripherally (*infra*).

35 In a specific embodiment, the compound designated No.

2016 reverses the soporific effect of R(-)-
alphamethylhistamine.

The data in the Examples, *infra*, support the view
5 that antagonists of histamine H₃-receptors of the
invention are useful regulators of the sleep-
wakefulness cycle with potentially useful cognitive
and behavioral effects in mammals including humans.

In vivo studies can be used to show effectiveness
10 of a compound of the invention to cross the blood-
brain barrier, as shown in the examples, *infra*. The
data support the view that drugs of the present
invention penetrate the blood brain barrier and are
able to exert beneficial central actions in mammals
15 when these drugs are administered to the peripheral
circulation.

5.3. THERAPY

The histamine H₃-receptor antagonists of the
20 invention can be provided therapeutically for the
treatment of a subject suffering from a cognitive
disorder or an attention or arousal deficit, according
to the present invention. One of ordinary skill in
the art would readily determine a therapeutically
25 effective dose of an H₃ receptor antagonist of the
invention based on routine pharmacological testing and
standard dosage testing. In one aspect of the present
invention, the compounds can be administered in doses
of about 0.01 to about 200 mg/kg, more preferably 1 to
30 100 mg/kg, and even more preferably 30 to 100 mg/kg.
In a specific embodiment, greater than about 20 mg/kg
of a compound of the invention was effective to reduce
the soporific effect of (R)α-methylhistamine.

Included in the routine pharmacological testing are
35 toxicity studies to determine an upper limit dose.

Such toxicity studies can include LD₅₀ studies in mice, and 15 day toxicity studies in mammals.

The histamine H₃-receptor antagonists of the invention are believed to increase the release of cerebral histamine, acetylcholine and serotonin. These compounds can lead to increased arousal and attention. They can also be of benefit in the treatment of cognitive disorders.

Therapy with a compound of the invention is indicated to treat dementia, as either a primary or an adjunct therapy. The compounds of the invention have clinical utility in the treatment of dementia disorders in general. In a preferred embodiment, a compound of the invention can be used in the treatment for Alzheimer's disease. The compounds can also be used to treat presenile and senile dementia, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, Tourette syndrome and Parkinson's disease, to name but a few. Other specific indications include the treatment of narcolepsy and hyperactivity in children. In another embodiment, the compounds of the invention can be used in the treatment of certain psychoses, for example forms of depression or schizophrenia.

The compounds of the invention can be used to arouse victims of comas induced by stroke, drugs or alcohol. In another embodiment, the compounds of the invention can be used to increase wakefulness, where this effect is desired. For example, the compounds of the invention, which are preferentially targeted to H₃ receptors in the brain, can be used to counteract the soporific effect of some antihistamines without negating the therapeutic effects of the antihistamines on peripheral tissue, e.g., lung. Thus allergy patients can relieve some of the side effects of

antihistamine therapy. Similarly, the compounds of the invention can be used to reverse overdose of barbituates and other drugs.

- 5 The effective dose of a compound of the invention, and the appropriate treatment regime can vary with the indication and patient condition, e.g., the treatment of a dementia or the treatment of tiredness may require different doses and regimens.
- 10 These parameters are readily addressed by one of ordinary skill in the art and can be determined by routine experimentation.

A therapeutic compound of the invention may also contain an appropriate pharmaceutically acceptable carrier or excipient, diluent or adjuvant, i.e., the compound can be prepared as a pharmaceutical composition. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium carbonate, magnesium stearate, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. These compositions can take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained-release formulations and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such

compositions will contain an effective therapeutic amount of the active compound together with a suitable amount of carrier so as to provide the form for proper 5 administration to the patient. While intravenous injection is a very effective form of administration, other modes can be employed, including but not limited to intraventricular, intramuscular, intraperitoneal, intra-arteriolar, and subcutaneous injection, and 10 oral, nasal and parenteral administration.

The therapeutic agents of the instant invention may be used for the treatment of animals, and more preferably, mammals, including humans, as well as mammals such as dogs, cats, horses, cows, pigs, guinea 15 pigs, mice and rats.

In another embodiment, the therapeutic compound can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

In yet another embodiment, the therapeutic 25 compound can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In 30 another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et 35

al., *Science* **228**:190 (1985); During et al., *Ann. Neurol.* **25**:351 (1989); Howard et al., *J. Neurosurg.* **71**:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

Other controlled release systems are discussed in the review by Langer (*Science* **249**:1527-1533 (1990)).

6. EXAMPLES

A series of compounds were prepared and tested for their histamine H₁ receptor antagonist activity. The results are summarized in Table 1. The antagonist activity of the compounds was detected by observing inhibition of (³H)-N-(alpha)methylhistamine activity on rat brain membranes.

20

6.1. SYNTHESIS OF THE COMPOUNDS

The amide and carbamate compounds of Table 1 were synthesized from 4-(4-piperidyl)-1H-imidazole by three general procedures:

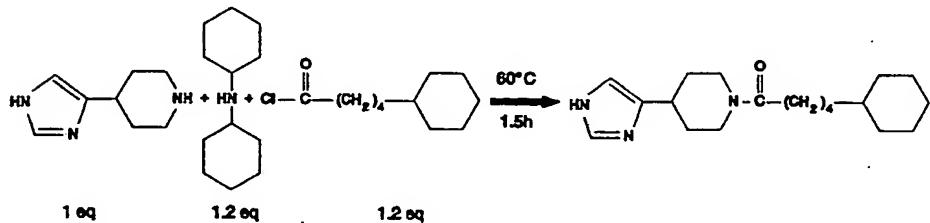
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Procedure A: 4-(4-piperidyl)-1H-imidazole and the appropriate acid chloride were conjugated using dicyclohexylamine as base according to the following scheme:

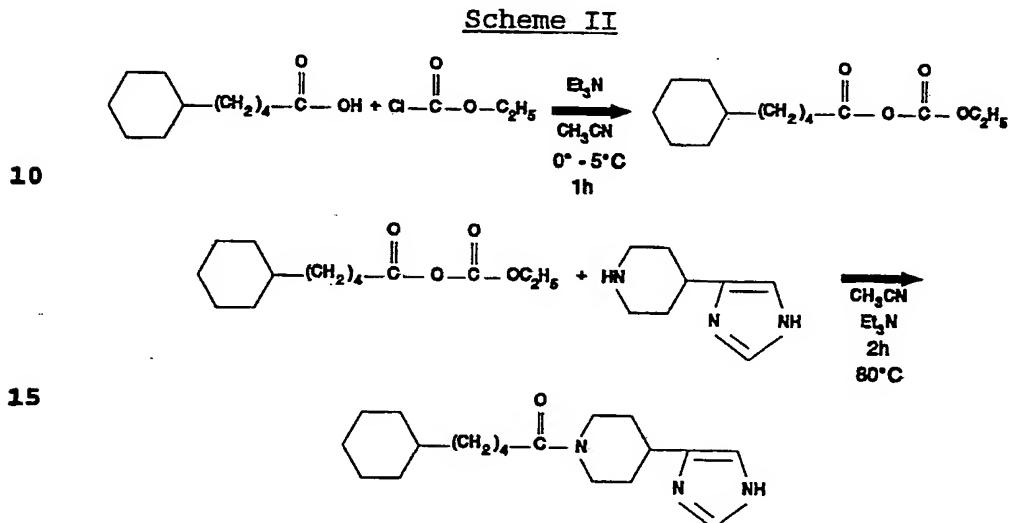
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Scheme I

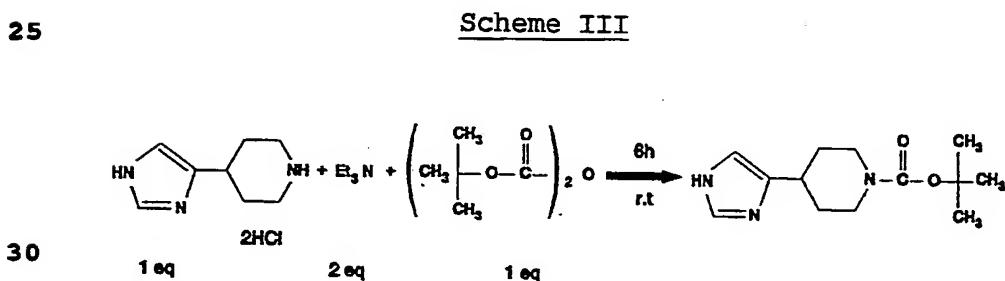
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Procedure B: 4-(4-piperidyl)-1H-imidazole and the corresponding acid anhydride were conjugated using triethylamine as base according to the following scheme:



20 Procedure C: 4-(4-piperidyl)-1H-imidazole and the corresponding dicarbonate were conjugated using triethyl amine as a base according to the following scheme:



6.1.1. PREPARATION OF 4-(1-CYCLOHEXYLVALEROYL-4-PIPERIDYL) 1H-IMIDAZOLE (COMPOUND 1)

To a mixture of 755 mg (5.00 mmol) 4-(4-piperidyl)1-H-imidazole and 942 mg (5.20 mmol) of dicyclohexylamine in 10 ml anhydrous acetonitrile at

25°C was slowly added 1.06 g (5.20 mmol) cyclohexanevaleryl chloride in 2 ml of dichloromethane over a period of 10 min with stirring; then the 5 reaction mixture was heated at 60°C for 1.5 h. After cooling to ambient temperature, the solid side product that was obtained (dicyclohexylammonium chloride) was filtered off and the filtrate was concentrated in vacuo to remove acetonitrile. The resulting crude oil 10 was crystallized with methanol: anhydrous diethyl ether to give 1.085 mg of analytically pure product as a yellow powder. Yield: 68%; M.P.: 159°C; MS: m/e=317 (M+); ^1H NMR (CDCl_3): imidazole H: δ 7.65 (s, 1H), 6.75 (s, 1H); cyclohexylbutyl: δ 2.20 (m, 8H), 15 1.20 (m, 11H); piperidyl: 4.65 (d, 2H), 3.95 (d, 2H), 3.10 (d, 2H), 2.84 (m, 1H), 2.20 (m, 2H).

Compounds No. 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 in Table I were synthesized in similar manner, i.e., by condensation of the acid chloride with 4-(4-piperidyl) 1-H-imidazole in the presence of dicyclohexylcarbodiimide. Purified product was obtained by preparative TLC Silica Gel GF. 60 (2000 Microns) and the solvent of recrystallization was methanol:anhydrous ether (20:80).

25 Compound No. 3, yield: 70%; oil; MS m/e 275 (M+); ^1H NMR (CDCl_3): imidazole H: δ 7.60 and 6.75 (s, 1H); piperidine H: complex, δ 4.65 (d, 2H), 3.90 (d, 2H), 3.10 (m, 3H), 2.10 (m, 2H); cyclohexyl acetyl H: δ 1.50 (m, 11H), 2.80 (m, 2H)..

30 Compound No. 4, yield: 67%; oil; MS: m/e 267 (M+); ^1H NMR (CDCl_3): imidazole H: δ 7.50 and 6.60 (s, 1H); piperidine H: complex, δ 3.90 (d, 2H), 2.80 (m, 3H), 2.55 (m, 2H), 1.80 (m, 2H); phenyl acetyl H: δ 7.10 (m, 5H), 1.50 (m, 2H).

35 Compound No. 5, yield: 71%; oil; MS: m/e 297 (M+); ^1H NMR (CDCl_3): imidazole H: δ 7.80 and 6.70 (s,

1H); piperidine H: complex, δ 4.60 (d, 2H), 3.80 (d, 2H), 3.10 (m, 3H), 1.80 (d, 2H); phenyl propyl H: δ 7.20 (m, 5H), 2.65 (m, 2H), 2.35 (m, 2H), 2.10 (m, 2H).

5 Compound No. 6, yield: 74%; oil; MS: m/e 289 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.70 and 6.80 (s, 1H); piperidine H: complex, δ 4.60 (d, 2H), 3.85 (d, 2H), 3.10 (m, 3H), 1.90 (m, 2H); cyclohexyl ethyl H: δ 1.10 (m, 11H), 2.00 (br, 2H), 2.20 (m, 2H).

10 Compound No. 7, yield: 75%; oil; MS: m/e 283 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.60 and 6.70 (s, 1H); piperidine H: complex, δ 4.60 (d, 2H), 3.90 (d, 2H), 3.10 (m, 3H), 1.80 (m, 2H); phenyl ethyl H: δ 7.30 (m, 5H), 2.10 (br, 2H), 1.50 (m, 2H).

15 Compound No. 8, yield: 69%; M.P.: 151°C; MS: m/e 327 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.65 and 6.80 (s, 1H); piperidine H: complex, δ 4.70 (d, 2H), 4.50 (d, 2H), 3.60 (m, 1H), 2.80 (m, 2H), 2.10 (m, 2H); adamantyl acetyl H: δ 1.80 (m, 12H), 3.10 (m, 2H), 20 4.05 (m, 1H).

Compound No. 9, yield: 62%; M.P.: 148°C (decomposed); MS: m/e 357 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.60 and 6.85 (s, 1H); piperidine H: complex, δ 4.50 (d, 2H), 4.05 (m, 3H), 3.40 (d, 2H), 25 2.10 (m, 2H); dicyclohexyl acetyl H: δ 1.50 (m, 22H), 2.50 (m, 1H).

Compound No. 10, yield: 64%; oil; MS: m/e 281 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.75 and 6.60 (s, 1H); piperidine H: complex, δ 4.70 (d, 2H), 4.20 (m, 3H), 2.80 (m, 2H), 2.10 (d, 2H); phenyl vinyl H: δ 7.40 (m, 5H), 6.50 (m, 2H).

Compound No. 11, yield: 62%; oil; MS m/e 351 (M+); 1 H NMR (CDCl₃): imidazole H: δ 7.50 and 6.40 (s, 1H); piperidine H: complex, δ 4.60 (d, 2H) 4.10 (m, 3H), 2.80 (d, 2H), 1.80 (m, 2H); phenyl cyclohexyl acetyl H: δ 7.20 (m, 5H), 1.80 (m, 11H), 3.70 (m, 1H).

Compound No. 12, yield: 72%; M.P.: 136°C; MS:m/e 304 (M+); ¹H NMR (CDCl₃): imidazole H: δ 7.70 and 6.80 (s, 1H); piperidine H: complex, δ 4.60 (d, 2H), 4.00 (m, 2H), 3.60 (m, 3H), 1.88 (m, 2H); cyclohexyl propyl H; complex, δ 1.20 (m, 17H).

6.1.2. ALTERNATIVE METHOD FOR THE PREPARATION OF 4-(1-CYCLOHEXYLVALEROYL-4-PIPERIDYL) 1H-IMIDAZOLE (COMPOUND 1)

10 Preparation of acid anhydride: Triethylamine (1.01 g, 10.00 mmol) was slowly added to a stirred solution of 1.84 g (10.00 mmol) cyclohexylpentanoic acid in 60 ml acetonitrile at 0°C. After 30 min. of stirring, 1.08 g (10.00 mmol) of ethylchloroformate 15 was added slowly in 5-7 min., so that the temperature remained between 0°C and 5°C. After 1h stirring, the solution was used for the preparation of Compound 1.

Preparation of Compound 1: The freshly prepared acid anhydride was poured into a suspension of 1.54 g 20 (10.20 mmol) of 4(4-piperidyl)imidazole and 1.03 g (10.20 mmol) triethylamine in 70 ml acetonitrile. After 1 h of heating at 80°C, the solution was concentrated under reduced pressure, and the oily residue was taken up with 75 ml water and then 25 extracted with 150 ml ethylacetate. The residual oil was obtained, which crystallized on addition of ethylacetate/hexane. Yield: 74%.

This method provides the desired amide in good yield when the piperidylimidazole is added in slight 30 molar excess, e.g., about a 1.01 to 1 molar ratio, to the asymmetric anhydride.

Compounds No. 52-58 in Table I were synthesized in similar manner, i.e., by condensation of the asymmetric ethylchloroformate acid anhydride with 4(4-35 piperidyl) 1H-imidazole in the presence of triethyl amine.

Commercially available 3,3-diphenylpropionic acid and 4,4-diphenylbut-3-enoic acid were used as the starting materials for compounds 52 and 54,
5 respectively. The unsaturated alkene bond of 4,4-diphenylbut-3-enoic acid was reduced under mild conditions by Pd/C (5%)/H₂ catalysis. This intermediate was then used to synthesize compound 53. Both intermediates 3,3-diclohexylpropionic acid and
10 4,4-dicyclohexylbutanoic acid, used in the preparation of compounds 55 and 56, respectively, were prepared by reduction of 3,3-diphenylpropionic acid and 4,4-diphenylbutanoic acid in the presence of catalyse Rh/alumina (5%)/H₂, 5 atm.

15 Compound No. 52, yield: 69%; MS.:M/e 359 (M+); ¹H NMR CDCl₃:imidazole H: δ 7.50 and 6.70 (s, 1H); piperidine H: complex δ 4.60 (d, 2H), 3.10 (m, 3H), 2.60 (d, 2H), 1.40 (m, 2H); propionyl H: complex δ 3.05 (m, 1H), 2.00 (d, 2H); biphenyl H: complex δ 7.20 (m, 10H), MA.: calc. C=76.85, H=7.00, N=11.68; found, 76.32, 6.72, 10.89, respectively.

Compound No. 53, yield: 73%; MS.:M/e 373 (M+); ¹H NMR CDCl₃:imidazole H: δ 7.65 and 6.70 (s, 1H); piperidine H: complex δ 4.60 (d, 2H), 3.00 (m, 2H), 2.50 (m, 2H), 1.80 (m, 2H); butanoyl H: δ 3.05 (m, 2H), 2.40 (m, 2H), 3.40 (m, 2H); diphenyl H: δ 7.10 (m, 10H).

Compound No. 54, yield: 64%; MS.:M/e 371 (M+); ¹H NMR CDCl₃:imidazole H: δ 7.40 and 6.50 (s, 1H);
30 piperidyl H: complex δ 4.50 (d, 2H), 3.60 (m, 3H), 3.20 (d, 2H), 1.50 (d, 2H); butenyl H: complex δ 6.70 (d, 1H), 3.50 (d, 2H); diphenyl H: δ 7.10 (m, 10H).

Compound No. 55, yield: 75%; MS.: M/e 371 (M+);
35 ¹H NMR CDCl₃:imidazole H: δ 8.00 and 7.10 (s, 1H); piperidyl H: complex δ 4.50 (d, 2H), 3.10 (d, 2H), 2.80 (m, 3H), 1.90 (d, 2H); propionyl H: complex δ

2.60 (d, 2H), 2.00 (m, 1H); dicyclohexyl H: complex δ 1.50 (m, 22H).

Compound No. 56, yield: 68%; MS.: M/e 385 (M+);
5 ^1H NMR CDCl₃: imidazole H: δ 8.00 and 7.05 (s, 1H);
piperidyl H: complex δ 4.50 (d, 2H), 3.80 (d, 2H),
3.00 (m, 3H), 2.10 (m, 2H); butanoyl H: δ complex 2.80
(m, 2H), 1.80 (m, 2H), 1.40 (m, 1H); dicyclohexyl H:
complex δ 1.20 (m, 22H).

10

6.1.3. PREPARATION OF 4-(t-BUTOXY CARBONYL-4-PIPERIDYL) 1H-IMIDAZOLE (COMPOUND 2)

To a suspension of 224 mg (1.00 mmol) of 4-(4-piperidyl)-1H-imidazole dihydrochloride in 10 ml of methanol was added 202 mg (2.00 mmol) of triethylamine (the suspension turned to a clear solution) followed by dropwise addition of 218 mg (1.00 mmol) of di-t-butyl dicarbonate in 5 ml methanol over a period of 10 min. The reaction mixture was stirred at 25°C for 6 h, at the end of which the volatile materials were removed in vacuo. The oily residue was partitioned between 50 ml chloroform and 25 ml water. The organic layer was washed with 50 ml brine solution, then dried over anhydrous sodium sulfate. After filtration and removal of solvent, a pale yellow oil was obtained.
15 The oil was treated with a mixture of methanol: petroleum ether (10:90). The resulting mixture was agitated vigorously with a glass rod until a solid appeared. After filtration and drying, the desired product was obtained as a white powder. Yield: 65%;
20 M.P.: 198°C; MS: m/e 251 (M⁺); ^1H NMR (CDCl₃): imidazole H: δ 7.60 (s, 1H) and 6.60 (s, 1H); piperidine H: δ 4.20 (d, 2H), 2.80 (m, 4H), 2.20 (d, 2H), 1.60 (m, 1H), t-BOC H: 1.45 (s, 9H).
25

Compounds No. 13 and 14 in Table I were synthesized in similar manner. The pure product was obtained by preparative TCL Silica GEL GF, 60 (2000

microns), and the solvent of recrystallization was methanol:anhydrous ether (20:80).

Compound No. 13, yield: 78%; M.P.: 180°C; MS: m/e 5 255 (M+); ¹H NMR (DMSO-d₆): imidazole H: δ 7.95 and 6.80 (s, 1H), NH: δ 7.80 and 6.60 (d, 1H); piperidine H: complex, δ 4.50 (d, 2H), 3.60 (m, 3H), 3.10 (m, 1H), 2.75 (m, 2H); phenyl H: δ 7.40 (m, 5H); MA: (C,H,N,): 70.36%, 6.71%, 16.30%.

10 Compound No. 14, yield: 72%; M.P.: 185°C; ¹H NMR (CDCl₃); imidazole H: δ 7.60 and 6.80 (s, 1H); piperidine H: complex, δ 4.50 (d, 2H), 3.00 (m, 3H), 2.05 (d, 2H), 1.60 (m, 2H); t-butyl H: δ 1.10 (s, 9H).

15 6.1.4. PREPARATION OF 4(-4-PIPERIDYL)-
1H-IMIDAZOLE

In a preferred embodiment, 4(4-piperidyl)-1H-imidazole for use in the synthesis of the H₃-receptors antagonists is prepared according to the following method.

20 Bromination of 4-acetyl piperidine (Aldrich) in hydrogen bromide/acetic acid was performed as described (Barlin *et al.*, Aust. J. Chem 42:735 (1989)).

25 A mixture of 11.23g (4.00 mmol) of bromoacetyl pyridine and 3.98 ml (10.0 mmol) formamide were fused together at 110°C with stirring for 4h. The crude reaction mixture was then concentrated on the rotary evaporator to remove volatile matter. The residue was dissolved in 50 ml methanol, and to this solution was added 100 ml anhydrous dimethyl ether slowly with stirring, which led to the formation of a brown precipitate. After stirring for another 0.5h, the precipitate was filtered, washed with 50 ml anhydrous ether and dried. This solid residue was dissolved in 20 ml water and the aqueous solution was basified to pH 9 with sodium carbonate. To this solution was

- 29 -

added 150 ml absolute ethanol slowly with stirring till a solid formed, which was filtered off. The filtrate was heated to boiling, then treated with 5 activated carbon and filtered. The filtrate was concentrated on rotary evaporator to dryness. Yield: 3.36g 58%; M.P.: 152°C (decomposed); MS: m/e 145 (M+), ¹H NMR (D₂O): imidazole H: δ 7.80 (s, 1H) and 7.20 (s, 1H); pyridyl H: 8.10 (d, 2H), 7.17 (d, 2H). The 10 pyridyl moiety was reduced by catalytic hydrogenation using 5-10% rhodium on carbon in acidified water at 20-55 atmospheres as described (Schunack, Archiv. Pharma. 306:934 (1973)).

15 6.2. ANTAGONIST ACTIVITY IN VITRO

The various compounds were tested for the ability to bind to the histamine H₁ receptor. A binding assay in a rat brain membrane preparation, based on inhibition of binding of [³H]-N-alpha-methylhistamine 20 using excess unlabeled alpha-methylhistamine to account for nonspecific binding, was developed. Total, specific and nonspecific binding of [³H]-N-alpha-methylhistamine to brain membranes is shown in FIG. 1. The K_d value was 0.19 nM in this preparation and the 25 nonspecific binding was less than 20% of the total binding at the K_d value. The compounds thioperamide (Arrang et al., *Nature* 327:117-123 (1987)) and burimamide (Black et al., *Nature* 236:385-390 (1972)) were tested as controls for this assay. The results 30 are shown in Table I.

TABLE I

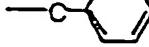
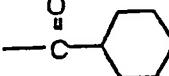
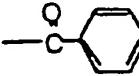
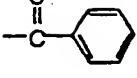
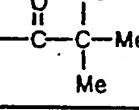
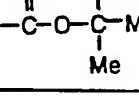
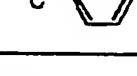
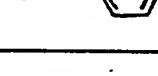
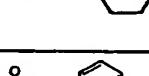
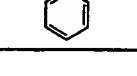
4-Piperidyl (imidazole) Compounds and
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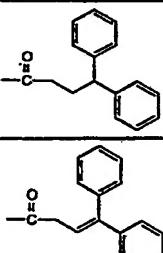
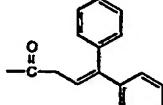
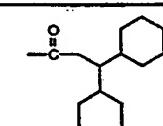
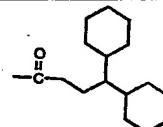
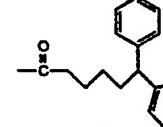
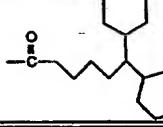
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($^3\text{H-N}^\alpha\text{-methylhistamine}$ as Radioligand)

	Cmpd No.	R ₁	X (= CO-(O) _n (CH ₂) _m R)	IC ₅₀ (nm)	M.P.
10	Thioperamide	H		4.0±0.6 n=4	170°C
			Burimamide	156±57	
15	1	H		23±6 n=3	159°
20	1	H		19±12 n=3	Oil
25	4	H		1400±437 n=3	Oil
30	5	H		262±9 N=3	Oil
	6	H		34±1.4 n=3	Oil
35	7	H		34.1±3.6 n=3	Oil
	12	H		41.4±9 n=3	136°C

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Cmpd No.	R ₁	X (= CO-(O) _x (CH ₂) _n R)	IC ₅₀ (nm)	M.P.
5	13	H		151±44 n=4
10	41	H		inactive n=2(1μM)
15	42	CH ₃		inactive n=2(1μM)
20	43	X		inactive n=3
25	44	X		inactive n=2
30	45	X		inactive n=2
35	46	PhCH ₂		inactive n=2
40	47	H		231 n=1
45	48	H		inactive n=2
50	52	H		93.1

Cmpd No.	R ₁	X (= CO-(O) _x (CH ₂) _y R)	IC ₅₀ (nm)	M.P.
5	H		124	oil
10	H		1000	158°C decomp.
15	H			118°C decomp.
20	H			152°C decomp.
				
				

25

30

35

Cmpd. No.	Structure	$IC_{50}(\text{Nm})$	M.P.
5 50		inactive $n=2(\mu\text{M})$	148.5°-150.5°C
10 2		243.5 ± 1.9 $n=2$	198°C
15 14		inactive $n=2$	185°C
20 8		inactive $n=2$	151°C
25 9		inactive $n=2$	148°C
30 10		570 ± 172 $n=3$	Oil
35 11		260 ± 38 $n=2$	Oil
51			115°C

6.3. DISCUSSION

The results in Table I show that the compounds of the invention are effective for binding to the histamine H₃-receptor. Interestingly, cyanoguanidine derivatives (e.g., compounds 47, 48 and 50) were ineffective at binding to the H₃-receptor. This result is in contrast to earlier observations about H₂-receptor antagonists. With H₂-receptor antagonists, cyanoguanidine and thiourea-containing derivatives (cimetidine and metiamide, respectively) were found to be bioisosteres, i.e., functionally substantially equivalent (Brimblecombe et al., *Gastroenterology* 74: 339-347 (1978)).

15

7. PHARMACOLOGICAL EVALUATION IN THE CNS

A representative compound, 1, was tested *in vivo* for (1) the ability to penetrate the blood brain barrier; and (2) the effect of behavior in mice.

20

7.1. PENETRATION OF THE BLOOD-BRAIN BARRIER

Blood-brain barrier penetration in rats was assessed by an *ex vivo* binding procedure. Young adult male Long-Evans rats were injected i.p. with saline or H₃ antagonists in saline. At various times after injection animals were sacrificed, the cortex was removed, homogenized in 50 mM Na/K-phosphate buffer, pH 7.4, and the binding of 1 nM [³H]-N^α-methylhistamine was measured using 400 µg protein of the homogenate. Nonspecific binding was accounted for by the inclusion of excess thioperamide in some samples. Under these conditions, the binding was approximately 90% specific.

As shown in FIG. 2, thioperamide at doses of 2, 5, and 10 mg/kg, when measured 15 min after injection, decreased the binding of [³H]-N^α-methylhistamine to H₃,

receptors in the cortex. This means that the thioperamide at these doses and after this time was able to penetrate the blood-brain barrier. Figure 3
5 shows that compound 1 also penetrates the blood-brain barrier one hour after injections of doses of 50 and 70 mg/kg. Taking into account the difference in affinity comparing thioperamide (4.0 nM) and compound 1 (23 nM), these data suggest that compound 1
10 penetrates the blood-brain barrier at least as well as thioperamide.

7.2. BEHAVIORAL EFFECTS IN MICE

The overall strategy to show central nervous
15 system antagonist activity was to challenge effects of the agonist (R) α -methylhistamine. Therefore, the first objective was to establish a dose response curve for behavioral effects of (R) α -methylhistamine. Male albino CF-1 mice weighing 20-30 g were used. Saline
20 or (R) α -methylhistamine in saline was injected i.p. in a volume \leq 0.4 ml. Animals were observed for various behaviors three times for 10 seconds during each 10 minute interval for a total of 2 hours. Animals were scored for the presence (1) or absence (0) of the
25 behavior and the results were reported as the accumulated score for a 30 minute period (maximum score = 9). As shown in FIG. 4, (R) α -methylhistamine produced a dose-dependent (range of 15 to 35 mg/kg) increase in sleeping one hour after injection. The
30 effect was also evident at 30 minutes after injection.

To assess the effects of antagonists, they were administered with the (R) α -methylhistamine in saline. FIG. 5 shows that thioperamide was able to inhibit the soporific effect of 30 mg/kg of (R) α -methylhistamine.
35 With thioperamide alone (i.e., in the absence of the α -methylhistamine H₁ receptor agonist), animals were

very active, exhibiting normal behaviors. FIG. 6 shows that compound 1 inhibited the soporific effect of 25 mg/kg (R)α-methylhistamine.

5

7.3. DISCUSSION

The results of the *in vitro* (see section 6, *supra*) and *in vivo* activity assays show that a compound of the invention is useful for increasing histamine activity in the brain.

In the foregoing *in vivo* assays, thioperamide was used as a positive control. The results indicate that compound 1 is effective as an H₁-receptor antagonist. Direct comparison of the two compounds is not available from the data, however, since the experimental protocols used to test each were not identical.

It is noteworthy that in all testing to date, no toxicity of the 1 compound has been observed, even at high doses.

8. SPECIFICITY OF COMPOUND 1

The selectivity of action of compound 1 for histamine H₁-receptors was determined in a NOVASCREEN™ receptor selectivity study. At concentrations of 10⁻⁵ M, no significant binding to adenosine, excitatory or inhibitory amino acid, dopamine, serotonin, or a broad range of petidergic receptors, or to ion channel proteins, peptide factor or second messenger systems was observed. The binding study results are shown in Table II.

TABLE II
NOVASCREEN® RECEPTOR SELECTIVITY ASSAY

				Initial Percent Inhibition (Average; N=2)
	Receptor/ Selectivity	Reference Compound	Reference K _i (nM)	10^{-5} M
5				
10	<u>Adenosine</u>	NECA	120.00	-3.0
	Adenosine			
	<u>Amino Acids</u>			
15	<u>Excitatory</u>			
	Quisqualate	Quisqualic Acid	11.80	-1.8
	Kainate	Kainic Acid DME	24.93	42.1
	MK-801	MK801	4.30	-8.6
	NMDA	NMDA	359.00	-4.5
	PCP	PCP	62.30	9.7
	Glycine	Glycine	300.00	1.8
20	<u>Inhibitory</u>			
	Glycine	Strychnine Nitrate	33.50	17.4
	GABA _A	GABA	2.80	0.6
	GABA _B	GABA	176.00	0.0
	Benzodiazepine	Clonazepam	3.40	2.7
	<u>Biogenic Amines</u>			
25	Dopamine 1	Butaclamol	37.30	6.4
	Dopamine 2	Spiperone	0.08	3.5
	Serotonin 1	Serotonin	4.60	-3.6
	Serotonin 2	Serotonin	531.00	10.5
	<u>Peptides</u>			
30	Angiotensin	Angiotensin II	0.20	6.5
	Arg-Vasopressin V ₁	arg-Vasopressin	4.90	10.1
	Bombesin	Tyr4-Bombesin	0.55	-5.5
	CCK Central	CCK	0.13	18.6
35	CCK Peripheral	CCK	0.02	6.9
	Substance K	Neurokinin A	2.75	29.2
	Substance P	Substance P	0.08	20.0
	NPY	Neuropeptide Y	0.50	-8.7
	Neurotensin	Neurotensin	1.23	-10.5
	Somatostatin	Somatostatin	0.03	4.1
	VIP	VIP	1.53	17.1

	Receptor/ Selectivity	Reference Compound	Reference K_i (nM)	Initial Percent Inhibition (Average; N=2)	
					$10^{-5}M$
Channel Proteins					
10	Calcium	w-Conotoxin	0.01	1.9	
	Calcium	Nifedipine	1.60	8.1	
	Chloride	TBPS	112.40	-3.4	
	Potassium	Apamin	0.05	7.7	
Peptide Factors					
15	ANF (rat)	ANP	0.15	0.1	
	EGF	EGF	0.24	18.1	
	NGF	NGF	0.80	17.1	
Second Messenger Systems					
20	Adenylate Cyclase	Forskolin	29.40	2.1	
	Forskolin				
25	Protein Kinase C				
	Phorbol Ester	PDBU	16.50	0.9	
	Inositol Triphosphate	IP3	12.50	9.2	

Values are expressed as the percent inhibition of specific binding and represent the average of duplicate tubes at each of the concentrations tested. Bolded values represent inhibition of fifty percent or greater.

- 39 -

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

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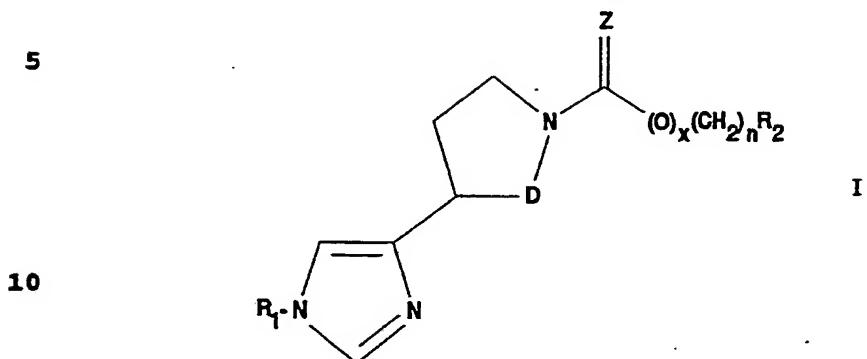
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WHAT IS CLAIMED IS:

1. A compound of the formula:



wherein R₁ represents hydrogen, an in vivo hydrolyzable group, an alkyl group, an cyclic alkyl group, or an aryl group; D is CH₂ or CH₂CH₂; Z is S O; x is 0 or 1; n is an integer from 0 to 6; and R₂ represents a substituted or unsubstituted linear chain or branched chain alkyl group of up to about 20 carbon atoms, a substituted or unsubstituted carbocyclic group of up to about 20 atoms, or a substituted or unsubstituted aryl group of up to about 20 carbon atoms, and salts thereof, with the provisos that if R₂ is tert-butyl, cyclohexyl, or dicyclohexylmethyl, x or n must not be 0; and if R₂ is adamantane, the sum of x and n must be greater than 1.

2. The compound according to claim 1 wherein n is an integer from 3-5.

30 3. The compound according to claim 2 wherein n is 4.

35 4. The compound according to claim 1 wherein
Z = 0.

5. The compound according to claim 4 wherein n
is an integer from 3-5.

5 6. The compound according to claim 5 wherein n
is 4.

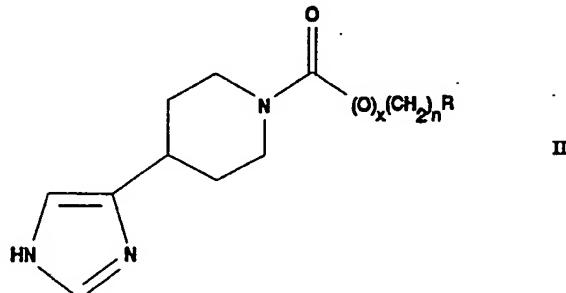
7. The compound according to claim 1 wherein R₂
is selected from the group consisting of cyclohexyl,
10 benzyl, adamantyl, dicyclohexylmethyl, diphenylmethyl,
cyclohexylphenylmethyl and cinnamoyl.

8. The compound according to claim 1 wherein X
is 1 and R₂ is t-butyl.

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9. A compound of the formula:

20



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wherein x is 0 or 1; n is an interger from 0 to 6; and
R represents a substituted or unsubstituted linear
chain or branched chain alkyl group of up to about 20
30 carbon atoms, a substituted or unsubstituted
carbocyclic group of up to about 20 carbon atoms, or
substituted or unsubstituted aryl group of up to about
20 carbon atoms, and salts thereof with the provisos
that if R is tert-butyl, cyclohexyl, or dicyclo-
35 hexylmethyl, x or n must not be 0; and if R is
adamantane, the sum of x and n must be greater than 1.

10. The compound according to claim 9 wherein n is an integer from 3 to 5.

5 11. The compound according to claim 10 wherein n is 4.

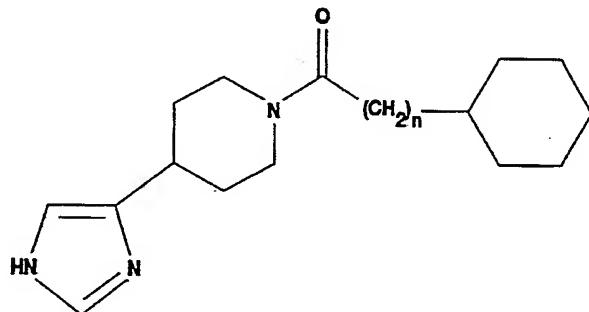
10 12. The compound according to claim 9 wherein R is selected from the group consisting of cyclohexane, benzene, adamantane, dicyclohexylmethyl, diphenylmethyl, cyclohexylphenylmethyl and cinnamoyl.

13. The compound according to claim 9 wherein x is 1 and R is t-butyl.

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14. A compound of the formula:

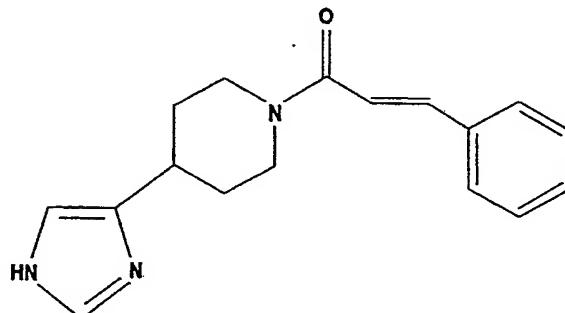
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25 in which n is 1, 2, 3 or 4.

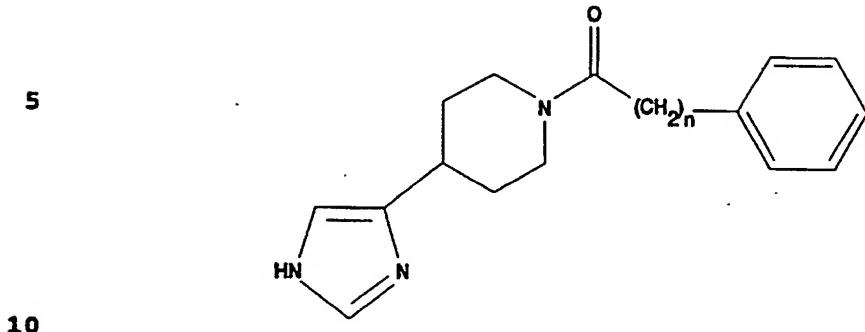
15. A compound of the formula:

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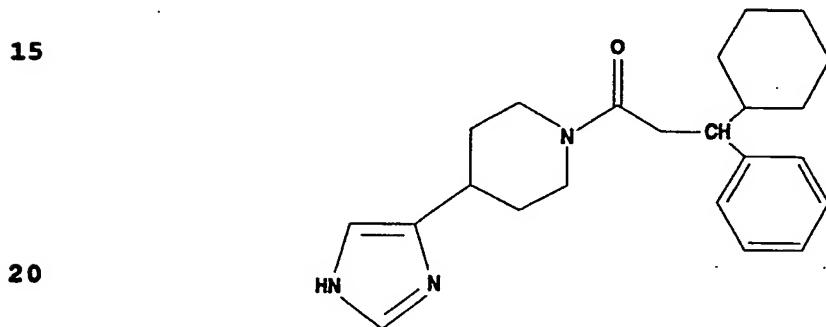
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16. A compound of the formula:



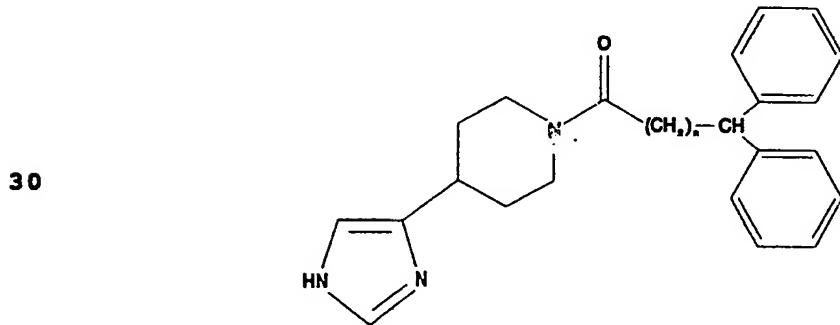
wherein n is 0, 1, 2, 3 or 4.

17. A compound of the formula:



25

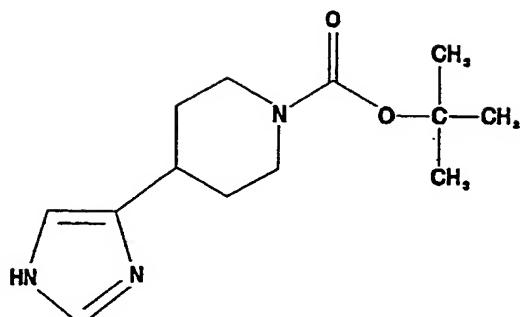
18. A compound of the formula:



in which n is 1, 2, 3 or 4.

19. A compound of the formula:

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20. A pharmaceutical composition comprising an amount of the compound according to claim 1 effective 15 to enhance a cognitive process, and a pharmaceutically acceptable carrier or excipient.

21. A pharmaceutical composition comprising an amount of the compound according to claim 9 effective 20 to enhance a cognitive process, and a pharmaceutically acceptable carrier or excipient.

22. A pharmaceutical composition comprising an amount of the compound according to claim 14 effective 25 to enhance a cognitive process, and a pharmaceutically acceptable carrier or excipient.

23. A pharmaceutical composition comprising an amount of the compound according to claim 16 effective 30 to enhance a cognitive process, and a pharmaceutically acceptable carrier or excipient.

24. A pharmaceutical composition comprising an amount of the compound according to claim 18 effective 35 to enhance a cognitive process, and a pharmaceutical acceptable carrier or excipient.

25. A method of treating a subject suffering from a cognitive disorder or an attention or arousal deficit comprising administering an amount of the 5 compound of claim 1 effective to treat the cognitive disorder or increase arousal or attention.

26. A method of treating a subject suffering from a cognitive disorder or an attention or arousal 10 deficit comprising administering an amount of the compound of claim 9 effective to treat the cognitive disorder or increase arousal or attention.

27. A method of treating a subject suffering 15 from a cognitive disorder or an attention or arousal deficit comprising administering an amount of the compound of claim 14 effective to treat the cognitive disorder or increase arousal or attention.

20 28. A method of treating a subject suffering from a cognitive disorder or an attention or arousal deficit comprising administering an amount of the compound of claim 16 effective to treat the cognitive disorder or increase arousal or attention.

25

29. A method of treating a subject suffering from a cognitive disorder or an attention or arousal deficit comprising administering an amount of the compound of claim 18 effective to treat the cognitive 30 disorder or increase arousal or attention.

30. The method of claim 25 in which the subject has Alzheimer's disease; a coma induced by stroke, drugs or alcohol; or narcolepsy.

35

31. The method of claim 26 in which the subject has Alzheimer's disease; a coma induced by stroke, drugs or alcohol; or narcolepsy.

5

32. The method of claim 27 in which the subject has Alzheimer's disease; a coma induced by stroke, drugs or alcohol; or narcolepsy.

10 33. The method of claim 28 in which the subject has Alzheimer's disease; a coma induced by stroke, drugs or alcohol; or narcolepsy.

15 34. The method of claim 29 in which the subject has Alzheimer's disease; a coma induced by stroke, drugs or alcohol; or narcolepsy.

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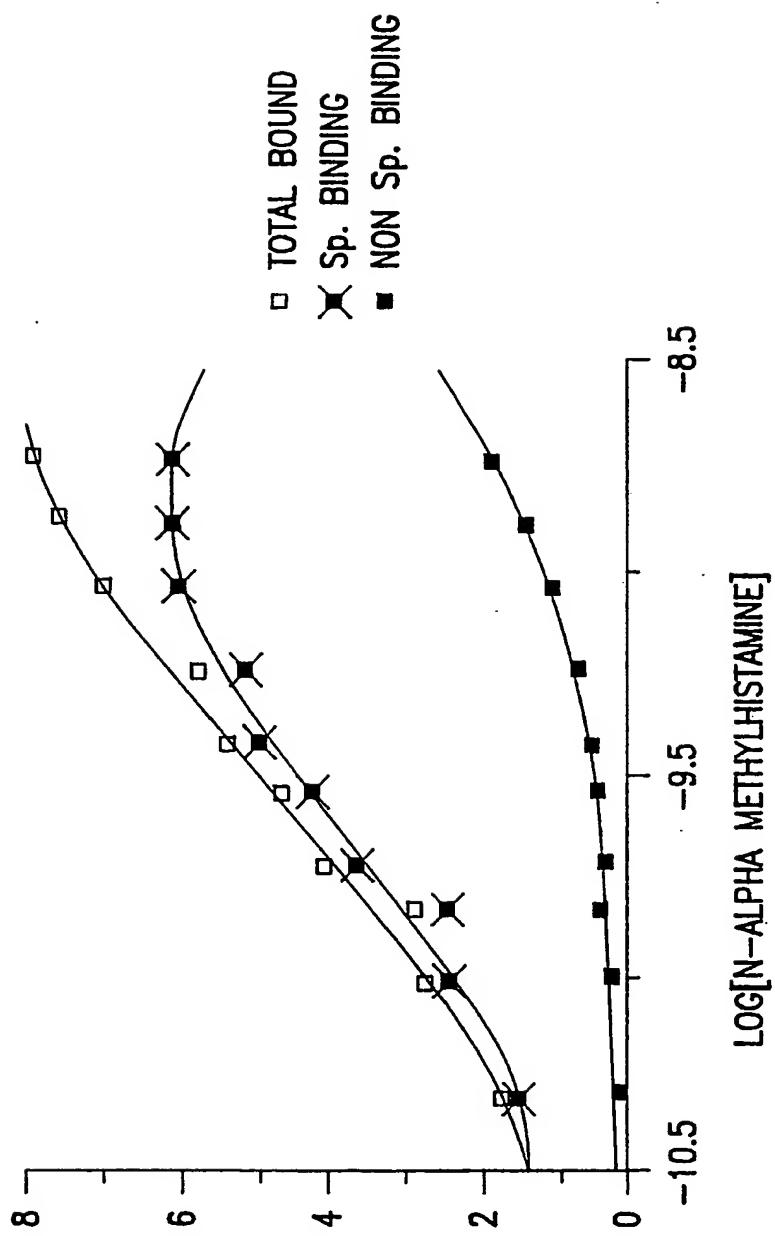


FIG. 1

SUBSTITUTE SHEET

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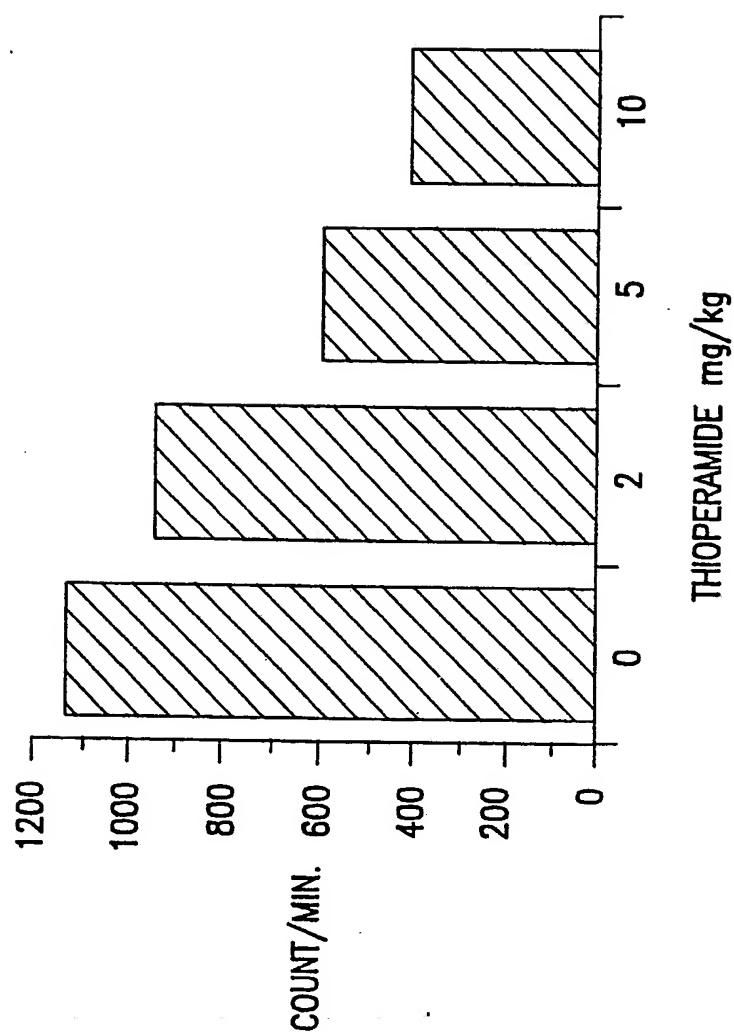


FIG. 2

SUBSTITUTE SHEET

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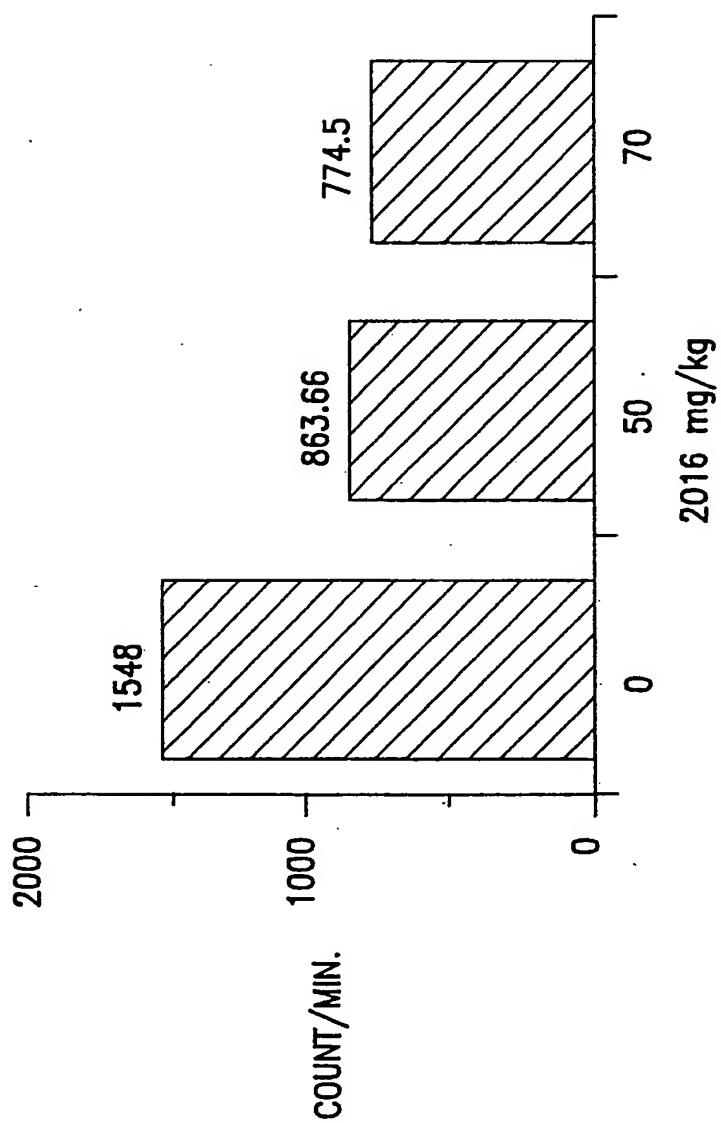


FIG.3

SUBSTITUTE SHEET

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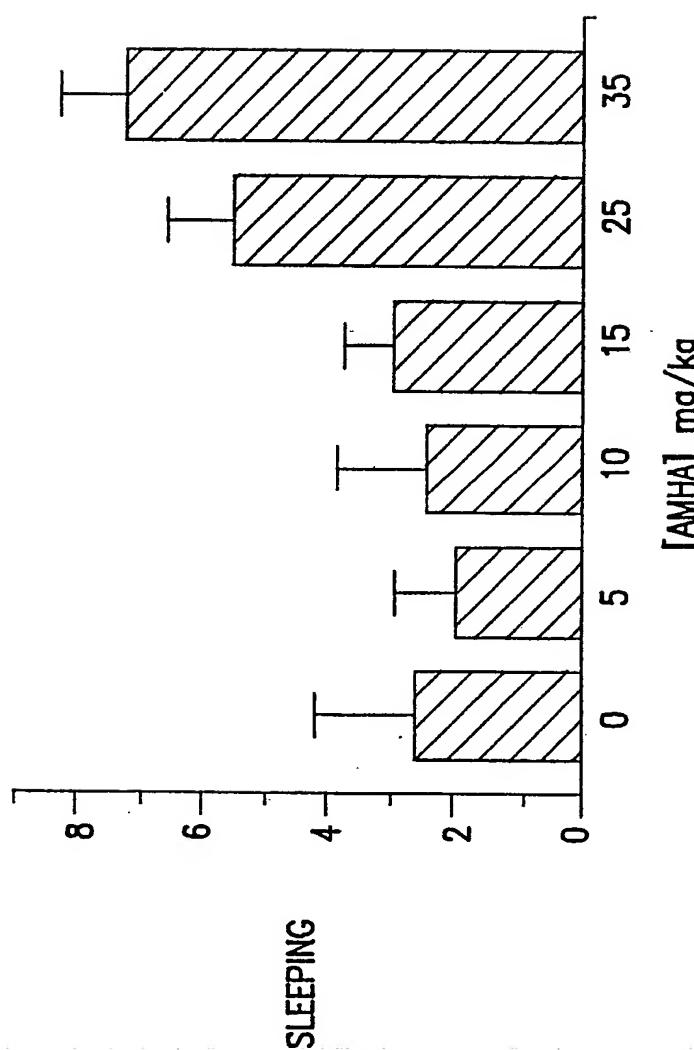


FIG. 4

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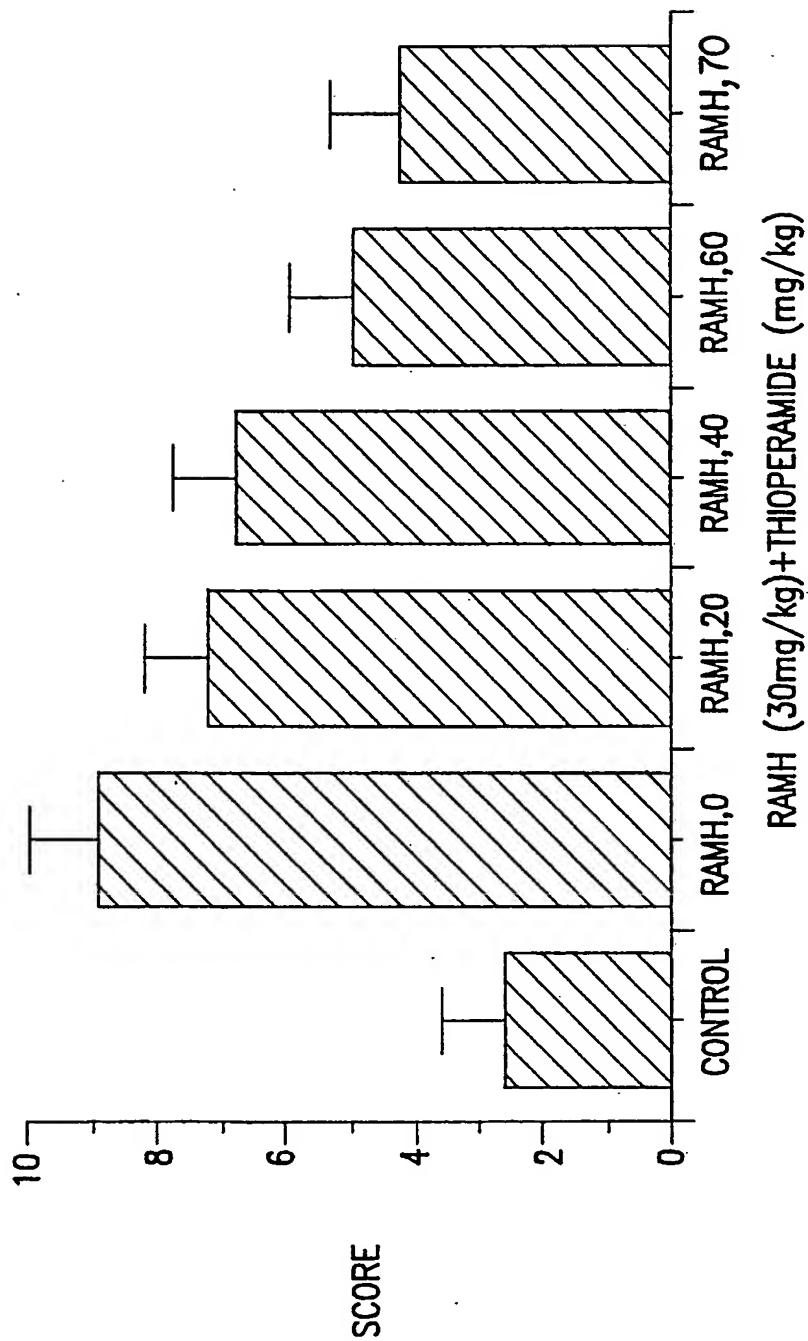


FIG.5

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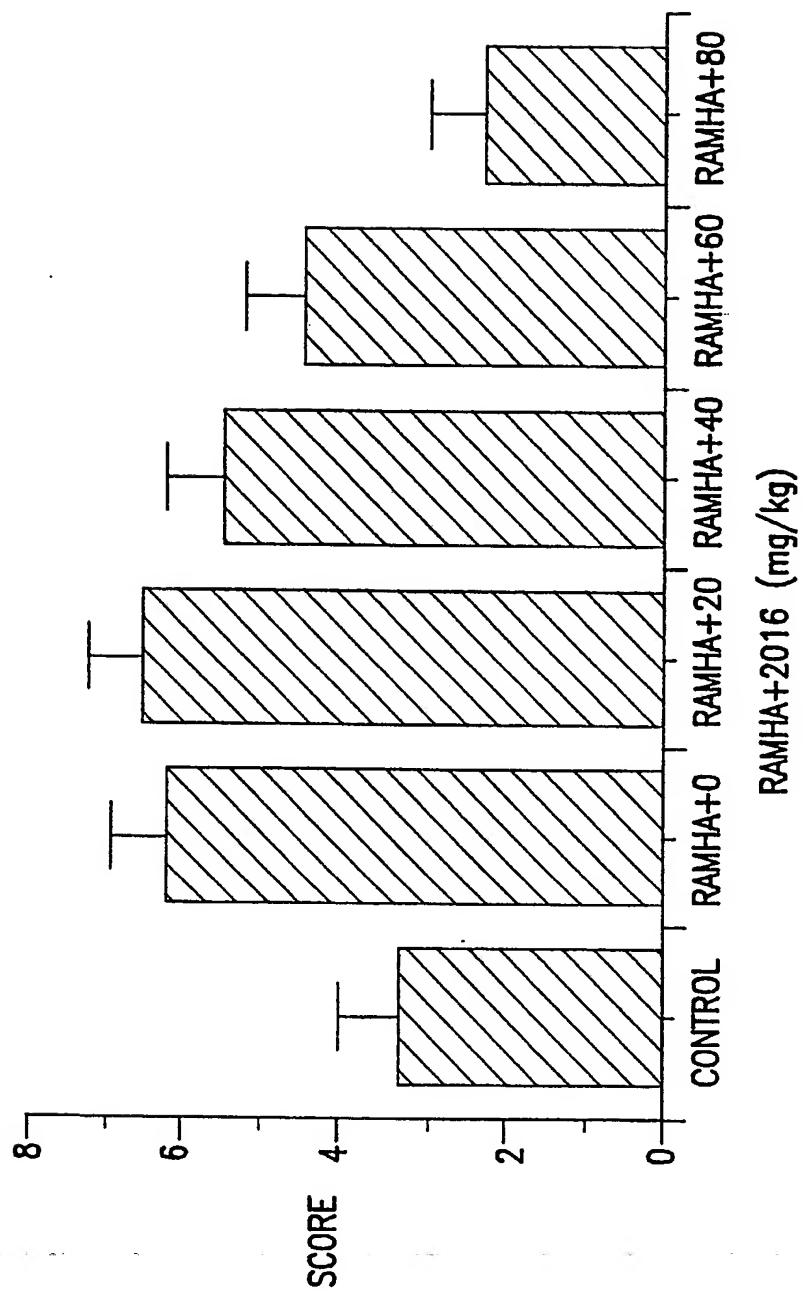


FIG. 6

SUBSTITUTE SHEET

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 93/03104

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.C1. 5 C07D401/04; C07D403/04; A61K31/415; A61K31/445

II. FIELDS SEARCHED

Minimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1. 5	C07D

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched⁸III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
P,X	EP,A,0 494 010 (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MEDICALE) 8 July 1992 see the whole document ----	1-24
A	EP,A,0 197 840 (INSTITUT NATIONAL DE LA SANTÉ ET DE LA RECHERCHE MEDICALE) 15 October 1986 see the whole document ----	1-24
A	NATURE vol. 302, 1983, LONDON GB pages 832 - 837 ARRANG J. M. ET. AL. cited in the application see the whole document ----	1-24 -/-

⁶ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
17 JUNE 1993	- 7. 07. 93

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Bernd Kissler

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	NATURE vol. 327, 1987, LONDON GB pages 117 - 123 ARRANG J. M. ET. AL. cited in the application see the whole document -----	1-24

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/03104

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-34 are directed to a method of treatment of (diagnostic method practised on) the human/animal body., the search has been carried out and based on the alleged effects of the compound/composition
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9303104
SA 72390

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 17/06/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0494010	08-07-92	FR-A-	2671083	03-07-92
		CA-A-	2058563	01-07-92
EP-A-0197840	15-10-86	FR-A-	2579596	03-10-86
		JP-A-	61267574	27-11-86
		US-A-	4707487	17-11-87